DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M20814

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

CBER 99 - 001

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WARNING LETTER

CERTIFIED - RETURN RECEIPT REQUESTED

Mr. Bo Poulsen
Pharmacia & Upjohn, Hillerod A/S
Herredsvejen 2 DK-3400
Hillerod, Denmark

Dear Mr. Poulsen:

The Food and Drug Administration (FDA or the agency) conducted an inspection of Pharmacia & Upjohn, Hillerod A/S, located at Herredsvejen 2 DK-3400, Hillerod, Denmark, on June 15 through June 19, 1998. The inspection revealed deviations from Subchapter C, Part 211 and Subchapter F, Parts 600-680, Title 21, Code of Federal Regulations, (CFR), as follows:

1. Failure to withhold from distribution a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research [21 CFR 610.2(a)] in that allergenic patch test lot 90315 was shipped for distribution (December 16, 1997) prior to CBER lot release notification (February 5, 1998).

2. Failure to have written procedures describing the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)] in that:
   a. There is no approved component specification for the 1.5 inch plaster adhesive used in the manufacture of allergenic patch test lots 89492, 89518, 89590, 89677, 89714, 89856, 89915, 90007, 90047, 90087, 90165, 90191, 90244, and 90315.
   b. There is no documentation demonstrating the equivalency between the 1 inch plaster adhesive and the 1.5 inch plaster adhesive used since 1995.
   c. There is no documentation that CBER was notified of the [redacted] plaster adhesive component change [21 CFR 601.12].

3. Failure to establish and/or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to posses [21 CFR 211.100(a) and (b)]. For example:
   a. The written procedure entitled " [redacted] " is not followed in that during the investigation of lot 90315 the firm sampled and retested double the amount of samples required without a justification.
   b. The written procedure entitled "Monitoring of Particles in Special Areas of Zone 2" does not specify an adequate allowable time period to repeat monitoring when alert limits A1 are exceeded.
   c. The written procedure for microbial testing of distilled water used for washing and rinsing production equipment does not include a diagram of production drop points, and any corrective action for consecutive out of specifications results.
   d. No written procedure exists for failure investigation.

4. Failure to validate and document the accuracy, sensitivity, specificity, and reproducibility of test methods employed to determine satisfactory conformance to final specifications for each batch of drug product [21 CFR 211.165(e)] in that the analytical method for determination of [redacted] has not been validated using the 1.5 inch plaster adhesive.

5. Failure to maintain or follow written procedures for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of drug products [21 CFR 211.67(b)] in that:
   a. The fume hoods in the sheet preparation area (room [redacted]) have not been calibrated and are not included in the central automated monitoring system.
   b. There is no written procedure for the maintenance of the assembling machine used for the assembly of allergenic patch tests.

6. Failure to establish and/or follow written testing programs designed to assess the stability characteristics of drug products [21 CFR 211.166] in that the procedure does not include any corrective actions to be taken when the analytical test fails or an individual patch fails stability.

We acknowledge receipt of your July 3 and August 21, 1998, written responses which address the observations on the Form FDA 483 issued at the conclusion of the inspection. We will provide comments to your Form FDA 483 responses after we receive your response to this letter.

The above deviations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.